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TOPIC 17 – Electrophysiology, rythmology and pacing - D

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0179

Contribution of calcium to the catecholaminergic automatic activity of rat pulmonary veins

Pierre Bredeloux [Orateur], Elizabeth Aguettaz, Ian Findlay, Véronique Maupoil
Université François Rabelais Tours, CNRS FRE 3511-IPBC-Physiologie des Cellules Cardiaques et Vasculaires, Tours, France

Ectopic activity in cardiac muscle of pulmonary veins (PVs) is implicated in the induction of paroxystic atrial fibrillation in humans. We reported that noradrenalin (NA) can induce automatic activity as bursts of "slow" action potentials (CAA) in rat PVs. Although the organisation of this automatism differs from the continous activity generated in the sino-atrial node, the mechanisms implicated in the sinusal rhythm have to be investigated. We found that I_f/HCN currents were not involved. Therefore, this study investigates the contribution of Ca^{2+}.

Mechanical and electrical activity was recorded from rings and strips of PVs dissected from male Wistar rats. Automatic activity was induced by the superfusion of NA.

ICa_L block with 10^{-8} to 2.10^{-7}M diltiazem evoked a progressive concentration-dependant inhibition of CAA.

Increasing extracellular Ca^{2+} led to a reduction of burst duration, an increase in spike frequency and an increase in the interval between bursts. In 3 and 5mM $[Ca^{2+}]_o$ bursts of automatic activity ceased in respectively 40% and 75% of the preparations.

On the other hand, reducing $[Ca^{2+}]_o$ to 0.7mM or inhibition of SERCA with 50 µM cyclopiazonic acid, lead to the replacement of CAA as clearly defined bursts of action potentials with low frequency (~1 Hz) continuous activity.

Ryanodine (10^{-7}-10^{-5}M) retained CAA as bursts of slow action potentials but reduced burst duration, spike frequency and the interval between bursts. It had complex effects upon the membrane potentials recorded during and between bursts.

Conclusions: These results demonstrate a major contribution of extracellular Ca^{2+} in the induction of CAA. The sarcoplasmic reticulum seems to participate mainly to the organisation of CAA.

0043

Determination of the specific contribution of cardiac connexins in the regulation of gap junction channel make-up and action potential propagation

Thomas Desplantez [Orateur] (1), Priyanthi Dias (2), Katahrina Grikscheit (3), Nicholas J Severs (4), Ken Macleod (4), Emmanuel Dupont (5)
(1) LIRYC - Inserm U1045, Inserm, Pessac, France - (2) Imperial College, London, Royaume-Uni - (3) University of Marburg, Institute of Pharmacology, Marburg, Allemagne - (4) NHLI - Imperial College, London, Royaume-Uni - (5) Unversity of Surrey, Faculty of Health and Medical Sciences, Guildford, Royaume-Uni

Cardiac myocytes express connexins Cx40, Cx43, and Cx45 that form diverse gap junction channels (GJC) characterised by distinct electrical properties, which determine the propagation of the action potential (AP). As the relationship between the Cx make-up and their contribution to the AP propagation is poorly understood and difficult to elucidate *in vivo*, we developed Rat Liver Epithelial (RLE) and HL-1 cell models. RLE cells endogenously express Cx43 and were transfected to induce the expression of Cx40 (Ind40) or Cx45 (Ind45). Western blot and triton X-100 extraction analyses show that the higher the level of induction, the higher the expression of Cx40 and Cx45, and a higher junctional Cx43:Cx45 than Cx43:Cx40 ratio. Dual voltage clamp on Ind45 cell pairs show a 30% decrease of the cell-cell coupling gj, 0 at any level of induction. However, low induction of Cx40 decreases gj, 0 by 29%, but high induction increases gj, 0 by 26%. A voltage dependence characteristic of Cx43 GJC was observed in non-induced cells, which decreases in Ind40 and Ind45 cells. Induction of Cx45 suggests that here is more rectification than in Ind40 cells. Western blotting on HL-1 clones (#1,2,3,4,6) indicate a similar level of expression of Cx40 and Cx43, higher than Cx45 (Cx43:Cx45=Cx40:Cx45≈20). Only clone 2 expresses lower levels of Cx40 and Cx43. Micro-electrode arrays recordings show that clone 6 has the faster conduction velocity (CV), clone 2 the slower, but a similar gj, 0. Unexpectedly SiRNA Cx45 knock-down on clone 6 decreases CV by 57%, a larger decrease than Cx40 and Cx43 knock-down, 35% and 25%, respectively. However, double knock-down (Cx40+Cx43; etc.) similarly decreases CV by 40%. Our data suggest a dependence of AP propagation on Cxs co-expression pattern. Single channel recordings are ongoing to elucidate the contribution of each Cx type on GJC make-up and AP propagation. Importantly Cx45 seems to contribute more significantly than its low level of expression would suggest.

0178

Prognostic Value of Atrial Fibrillation Pattern in Heart Failure

S. Taillandier [Orateur], Laurent Fauchier, B. Lallemand, Nicolas Clementy, Bertrand Pierre, I. Lagrenade, A Bernard-Brunet, Dominique Babuty
CHU Trousseau, Cardiologie - Pole Coeur Thorax Vasculaire Hemostase, Tours, France

Atrial fibrillation (AF) and heart failure (HF) frequently coexist and are associated with an increased mortality. This study evaluated the prognosis of AF pattern in patients suffering from HF.

Methods: All AF patients seen in our institution between 2000 and 2010 were identified in a database. Among them, 1906 patients had both AF and HF: 1032 patients (54%) had preserved LVEF and 874 patients (46%) had a decreased LVEF; 1056 patients (55%) had non permanent AF (paroxysmal or persistent) and 850 (45%) had permanent AF.

Results: During follow up of 1035±1101 days, 377 patients died, 462 were readmitted to hospital for HF and 200 had stroke or thromboembolic events (TE). In the group of patients with decreased LVEF, there was no significant difference in the rate of death between patients with permanent or non permanent AF. In the group of patients with preserved LVEF, non permanent AF was associated with a decreased risk of death (RR=0.64, p=0.02). Whatever the LVEF, non permanent AF was associated with a lower risk of HF hospitalization (RR 0.70, p=0.0001). Stroke risk did not differ according to the pattern of AF whatever the LVEF. The independent predictors of death were older age (p=0.0005), LVEF <45% (p=0.03), absence of PM or ICD (p=0.04) and lack of treatment with beta-blocker (p=0.02). The independent predictors of hospitalization for HF were permanent AF (RR=1.7, p=0.002), older age (p=0.02), female sex (p=0.05), LVEF <45% (p=0.002), smoking (p=0.001), thyroid disease (p=0.01), presence of PM or ICD (p=0.03) and higher CHA_2DS_2-Vasc score (p=0.01).

Conclusion: In patients with AF and HF, the risk of admission for HF was lower in non permanent AF. The rate of death was lower in non permanent AF only in patients with LVEF ≥45%. Stroke risk does not differ according to pattern of AF, whatever the LVEF. These results suggest maintaining sinus rhythm in order to reduce the rate of readmission for HF, and to decrease mortality in patients with preserved LVEF.

0010

Impact of cardioversion on ventricular repolarization during persistent atrial fibrillation

Rania Hammami [Orateur] (1), Sana Ouali (2), Rim Gribaa (2), Sami Hammas (2), Slim Kacem (2), Ilyes Naffeti (2), Fehmi Remedi (2), Essia Boughzela (2)

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(1) Service de Cardiologie de Sfax - Tunisie, Sfax, Tunisie - (2) service de sardiologie de sahloul, Sousse, Tunisie

Purpose: Changes in the ventricular repolarization during atrial fibrillation (AF) reduction are poorly understood. The aim of this study is to analyze changes in variables analyzing ventricular repolarization immediately after return to sinus rhythm.

Methods: We analyzed 100 patients who were hospitalized for permanent AF and having recovered a stable sinus rhythm spontaneously or in response to therapy reduction. We measured QTc interval (Bazett), Tp-Te duration in DII just before cardioversion and immediately after restoration of sinus rhythm.

Results: We defined 4 groups: spontaneous restoration of sinus rhythm (group 1, n=36), antiarrhythmic therapy (group 2, n=32), electrical cardioversion (group 3, n=13), electrical cardioversion +antiarrhythmic therapy (group 4, n=19). All parameters remained similar before AF reduction (QTc, p=0.25, Tp-Te, p=0.28) among the fourth groups. After restoration of sinus rythm, ventricular repolarization parameter was significantly prolonged In all groups (QTc from to 422.65±60ms to 444.81±64 (p<0.001); Tp-Te from 64.46±23 to 83.4±36 (p=0.04)).

Electrical cardioversion with taking antiarrhythmic drugs, is characterized by the most increased QTc interval (p=0.04) after restoration of sinus rhythm. Moroever, we noted that there is a negative correlation (r=-0.56, p<0.001) between QTc prolongation and QTc duration at baseline.

Conclusions: These findings suggest electrical vulnerability immediately after restoration of sinus rhythm more important with electrical cardioversion. Particular caution should therefore be applied whenever class III antiarrhythmic drugs are administered.

0360

What pertinent parameter(s) to rule out paroxysmal atrial fibrillation (pAF) in stroke patients?

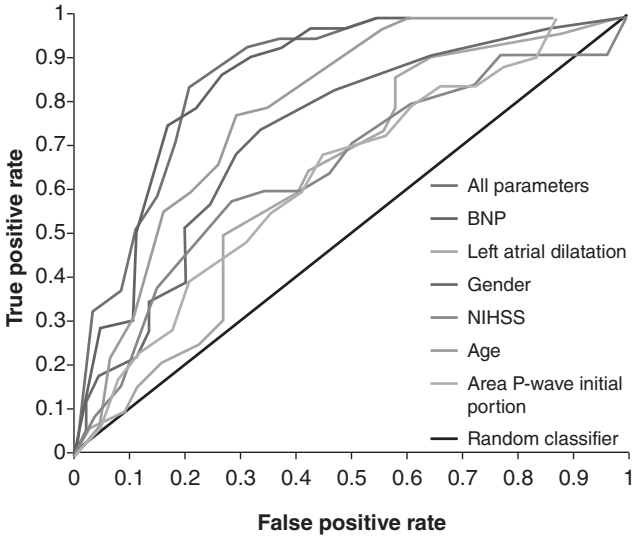
Laurent Suissa [Orateur] (1), Saskia Bresch (1), Sylvain Lachaud (1), David Bertora (2), Marie-Hélène Mahagne (1)
(1) Centre Hospitalier Universitaire de Nice, Unité Neurovasculaire, Nice, France - (2) Centre Hospitalier Universitaire de Nice, Service de Cardiologie, Nice, France

Background: Detecting paroxysmal atrial fibrillation (pAF) after ischemic stroke is challenging. The aim of the study was to compare diagnostic properties of all parameters associated to pAF.

Methods: We prospectively enrolled consecutive acute ischemic stroke patients admitted in stroke unit. Bedside Continuous ECG Monitoring (CEM) during hospitalization was systematically performed to detect pAF for naives AF patients on baseline ECG. All clinical and para-clinical data were collected. P-wave measures were performed on digitalized ECG (duration, amplitude, area, dispersion, initial and terminal force). Diagnostic value for all parameters significantly associated to pAF was assessed by comparisons of areas under receiver operating curves (AUC). Diagnostic properties were calculated at the Youden plot.

Results: Of the 200 patients included (age: 62.9+/-16.2, sex ratio: 1.4, NIHSS: 7.7+/-6.8, CEM duration 9.1 days), 45 (22.5%) were diagnosed in pAF. Parameters significantly associated to pAF were: age (p<0.0001), gender (p<0.0001), NIHSS (p=0.0038), BNP level (p<0.0001), left atrial dilatation (p<0.0001). For ECG analysis, area of P-wave initial portion in lead V1 emerged as independently associated to pAF (p=0.0136). Diagnostic value was classified by AUC (Figure 1): area of P-wave initial portion (0.641), left atrial dilatation (0.641), NIHSS (0.653), gender (0.694), age (0.794), BNP (0.861). The compilation of all the studied parameters (AUC: 0.872) did not add a supplementary diagnostic value compared to BNP alone. At Youden plot, diagnostic properties for BNP>135 pg/ml were (sensibility 91%, specificity 74%, negative predictive value 97%).

Conclusions: With its good predictive negative value, BNP≤135 pg/ml might rule out pAF in stroke patients. We suggest using it in clinical routine to help clinician to target stroke patients who might benefit from prolonged ECG monitoring.



ROC comparisons for parameters associated to AF.

0361

Optimal timing and duration of continuous ECG monitoring for detecting atrial fibrillation in stroke patients

Laurent Suissa [Orateur] (1), Saskia Bresch (1), Sylvain Lachaud (1), David Bertora (2), Marie-Hélène Mahagne (1)
(1) Centre Hospitalier Universitaire de Nice, Unité Neurovasculaire, Nice, France - (2) Centre Hospitalier Universitaire de Nice, Service de Cardiologie, Nice, France

Background: Several studies have suggested that after ischemic stroke, continuous ECG monitoring (CEM) increases the atrial fibrillation (AF) detection rate. However, optimal CEM terms of use are not clear so far and not widely accepted. The aim of our study was to define optimal duration and timing, in order to optimise AF detection rate.

Methods: We prospectively enrolled consecutive acute ischemic stroke patients admitted in stroke unit. Bedside Continuous ECG Monitoring (CEM) was systematically performed for AF naives patients on baseline ECG. 2 leads were recorded by Holter function and read daily by Neurologist. When AF (>30 s) was detected, the beginning and the end of the event were collected. Patients who underwent cardioversion during hospitalization were excluded. In this same cohort, areas under receiver operating curves (AUC) comparisons were performed between different terms of use to determine optimal timing and duration of CEM.

Results: Of the 373 patients included, 53 (14.2%) had AF on baseline ECG and were excluded. Of the 320 patients undergoing CEM during hospitalization (age: 63.5+/-15.6 y, sex ratio: 1.4, NIHSS: 8.7+/-8.6, CEM duration: 9.1 days), AF was diagnosed for additionally 52 patients (16.6%). No patients underwent cardioversion. Diagnostic value for CEM performed at admission was increased significantly with recording ECG duration (24h AUC=0.562, 48h AUC=0.892, 72h AUC=0.919). Correlation is not linear and the usefulness of CEM beyond 4 days is not significant. At equal duration, diagnostic value was significantly better when ECG recording was performed at admission than randomly during hospitalization (Figure 1).

Conclusions: Timing and duration of CEM are significantly associated with AF diagnostic rate. We suggest a widespread use of CEM in stroke units in order to enhance the AF detection. It must be started early in acute stroke patients, and prolonged over a minimal 4 days period.

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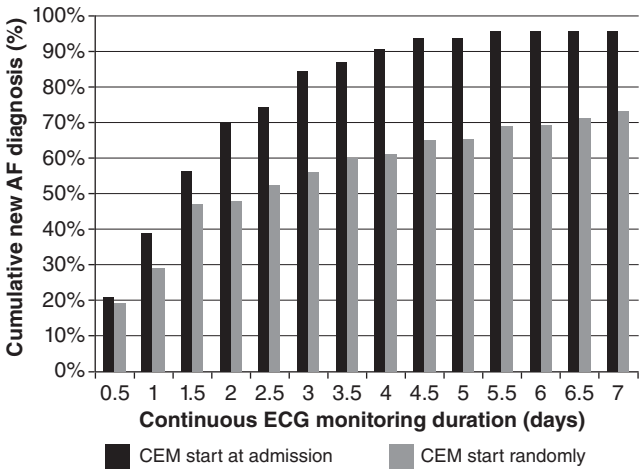

Cumulative new AF diagnosis in stroke patients.

0184

Role of endothelium on the catecholaminergic automatic activity and on the contractile and relaxant responses of rat isolated pulmonary veins

Bei Li Zhang [Orateur], Jean-Louis Freslon, Véronique Maupoil
Université François-Rabelais Tours, CNRS FRE 3511-IPBC-Physiologie des cellules cardiaques et vasculaires, Tours, France

Pulmonary veins have specific structural characteristics containing endothelium, smooth muscle and cardiac muscle. Previously, we have reported a catecholaminergic automatic activity (CAA) occurring in bursts in cardiac muscle within rat pulmonary veins. This study was designed to assess the role of endothelium on this CAA and to determine its role on the contractile and relaxant responses in rat isolated pulmonary veins.

The pulmonary venous rings were isolated from male Wistar rats. They were mounted in a Mulvany-Halpern myograph in Krebs-Heinseleit solution at 37°C for recording the contraction of cardiomycytes evoked by electrical field stimulation and for measurement of isometric tension of smooth muscle cells.

The removal of endothelium did not modify the incidence and the organisation (duration of the bursts, interval between the bursts) of CAA. Addition of 10^{-5} M sodium nitroprusside (SNP), a NO donor, in PV ring without endothelium did not modify the incidence of CAA but decreased the duration of the bursts. However, in PV rings with endothelium, inhibition of NO synthase by L-NAME (10^{-4} M) did not affect CAA.

Maximal contractile responses of smooth muscle cells were greater with the thromboxane receptor agonist U46619 (0.53±0.09g, 3 x 10^{-6} M) than with phenylephrine (0.25±0.05 g, 10^{-5} M) or cirazoline (0.25±0.04 g, 10^{-5} M). Strangely, the removal of endothelium reduced the vasoconstriction response to cirazoline (≈50%) but not those to U46619 or phenylephrine. Acetylcholine, an endothelium-dependent vasodilator, caused only about 10% relaxation of U46619 precontracted PV. However, the endothelium-independent vasodilators, SNP and isoprenaline were capable to induce a concentration-dependent relaxation in PV with a maximal relaxation of about 80% and 60% respectively.

These results suggest that in the rat isolated PV, endothelium play a minor regulatory role in the CAA as well as in the contractile responses to vasoconstrictor agents.

0140

Characterization of a new C-terminal truncating Nav1.5 mutation associated with sick sinus syndrome and atrial arrhythmia

Azza Ziyadeh-Isleem [Orateur] (1), Jerome Clatot (1), Sabine Duchatelet (1), Estelle Gandjbakhch (1), Isabelle Denjoy (2), Svetlana Maugenre (1), Françoise Hidden-Lucet (3), Alain Coulombe (1), Nathalie Neyroud (1), Pascale Guicheney (1)
(1) Inserm-UPMC UMR_S 956, Paris, France - (2) Hôpital Bichat, Service de cardiologie, Paris, France - (3) Hôpital Pitié-Salpêtrière, Service de cardiologie, Paris, France

Introduction: Mutations in *SCN5A*, which encodes the cardiac sodium channel Nav 1.5, result in multiple arrhythmic syndromes, like long QT syndrome type 3, Brugada syndrome, and rare cases of sick sinus syndrome and atrial fibrillation. Eight families with atrial arrhythmia were screened for twelve familial atrial fibrillation genes. A heterozygous *SCN5A* frameshift mutation, p. Arg1860GlyfsX12, leading to premature truncation of the Nav1.5 C-terminal domain, was identified in a family presenting with an atypical phenotype of sick sinus syndrome, paroxysmal atrial fibrillation, first degree AV block and atrial flutter. We aimed to characterize the physiological and biophysical properties of this mutation.

Methods and results: Sequencing and restriction analysis showed mutant mRNA to be present in proband lymphocytes, escaping nonsense mediated mRNA decay, consistent with the mutation's location in the last exon of *SCN5A*. The sodium current I_{Na} was recorded in HEK293 cells transfected with wild type (WT) or mutant channels using the patch-clamp technique. Mutant channel reduced I_{Na} by 70% compared to WT. In addition, gating kinetics analysis showed a 20-mV negative shift of inactivation and an increased late current. Western blot analysis showed a significant decrease in total protein expression of the mutant channel compared to WT. Mutant protein expression was restored by the ubiquitin-proteasome inhibitor, MG132, suggesting a cellular degradation of the mutant. Moreover, cell surface protein biotinylation showed reduced cell surface expression of mutant compared to WT.

Conclusion: The Nav1.5 mutant Arg1860GlyfsX12 resulted in a loss-of-function phenotype, with a mixed clinical picture of sick sinus syndrome, first degree AV block and atrial fibrillation or flutter. We now aim to determine the sub-cellular localization of this truncated channel which lacks binding sites for proteins involved in the correct localization and stability of the cardiac Na^+ channel.

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